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EFFICACY AND SAFETY OF TAPENTADOL EXTENDED RELEASE VERSUS OXYCODONE CONTROLLED RELEASE IN OPIOID-NAIVE AND OPIOID-EXPERIENCED PATIENTS WITH CHRONIC PAIN ASSOCIATED WITH OSTEOARTHRITIS OF THE KNEE

M. Etropolski[1], B. Lange[2], B. Kuperwasser[1], **K. Kelly**[1], A. Okamoto[1], A. Steup[2], I. Van Hove[3], H. Weber[2], J. Häussler[1]
[1]Johnson & Johnson Pharmaceutical Res. & Dev., L.L.C., Raritan, NJ; [2]Res. & Dev., Grünenthal GmbH, Aachen, Germany; [3]Johnson & Johnson Pharmaceutical Res. & Dev., Div. of Janssen Pharmaceutica, N.V., Beerse, Belgium

Purpose: To characterize the differential efficacy and safety of tapentadol extended release (ER) by prior opioid experience in patients with moderate to severe chronic osteoarthritis knee pain.
Methods: Patients were randomized to receive controlled, adjustable bid doses of tapentadol ER (100-250 mg), oxycodone HCl controlled release (CR; 20-50 mg), or placebo during a 12-week maintenance period preceded by a 3-week titration period. Patients were categorized by prior opioid use during the 3 months before screening. Change from baseline in average pain intensity was assessed (11-point numerical rating scale) for the overall maintenance period. Last observation carried forward was used to impute pain measurements that were missing after discontinuation of treatment.
Results: Opioid-naive patients represented 67.6% of the intent-to-treat population (n = 1,023). The least squares mean difference (LSMD; standard error of the mean [SEM]) from baseline in average pain intensity over the maintenance period in the opioid-naive groups was statistically superior to placebo with tapentadol ER (-0.7 [0.21]; *P*=0.001) but not with oxycodone CR (-0.3 [0.21]; *P*=0.139). Results were similar in the opioid-experienced groups (tapentadol ER vs placebo, LSMD [SEM] = -0.8 [0.32], *P*=0.014; oxycodone CR vs placebo, LSMD [SEM] = -0.5 [0.32], *P*=0.101). The rate of study discontinuation was lower in the tapentadol ER group than in the oxycodone CR group for opioid-naive (placebo, 35.0%; tapentadol ER, 41.7%; oxycodone CR, 68.8%) and opioid-experienced (placebo, 45.6%; tapentadol ER, 45.0%; oxycodone CR, 55.6%) patients. Rates of discontinuation due to adverse events (AEs) were as follows: for opioid-naive patients, placebo, 7.2%; tapentadol ER, 19.6%; oxycodone CR, 48.3%; for opioid-experienced patients, placebo, 5.3%; tapentadol ER, 18.3%; oxycodone CR, 31.5%. The incidence of overall and gastrointestinal-related treatment-emergent AEs were lower in the tapentadol ER group than in the oxycodone CR group, regardless of prior opioid experience (Table 1).
Conclusions: Tapentadol ER (100-250 mg bid) is an effective analgesic treatment with better overall and gastrointestinal tolerability than oxycodone CR (20-50 mg bid), regardless of prior opioid experience.

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ACCEPTABILITY OF A NOVEL 7 DAY BIMONTHLY PARTICIPANT DIARY IN A LONG-TERM CLINICAL TRIAL AMONG PEOPLE WITH SYMPTOMATIC KNEE OA

M. Agaliotis, L. Nairn, M. Votrubec, M. Fransen
Faculty of Hlth.Sci., Univ. of Sydney, Lidcombe, Australia

Purpose: To evaluate the participant acceptability of a cost-effective novel participant diary engineered to regularly capture relevant clinical outcomes and health economic data during the course of a long-term clinical trial.
Methods: A novel Participant Diary was developed for participants of a two year clinical trial evaluating the benefits of glucosamine, with or without chondroitin, in people with symptomatic knee osteoarthritis (OA). The Participant Diary was dispatched with the study treatment capsules every two months. The seven day diary required the daily recording of knee pain 'at its worst' (rated 0-10), overall global assessment of arthritis (excellent to poor; 0-4), participation in at least moderate physical activity for more than 20 minutes (yes/no), use of analgesia (name; daily

Abstract 328 – Table 1. TEAEs by Prior Opioid Experience

	Opioid-naive			Opioid-experienced		
	Placebo n=223	Tapentadol ER n=235	Oxycodone CR n=234	Placebo n=114	Tapentadol ER n=109	Oxycodone CR n=108
All TEAEs (%)	61.0	79.6	87.2	61.4	67.9	88.0
Gastrointestinal-related	25.6	47.7	67.5	27.2	33.0	66.7
Nervous system-related	24.2	43.4	50.0	26.3	33.0	43.5
Skin and subcutaneous tissue-related	3.1	13.6	22.2	4.4	16.5	17.6
Psychiatric-related	4.5	12.3	16.2	5.3	12.8	12.0
Musculoskeletal and connective tissue-related	17.9	9.8	9.4	16.7	11.9	13.0

TEAEs, treatment-emergent adverse events; ER, extended release; CR, controlled release.

dosage) and presenteeism (work capacity; 0-100%). Participants were also asked to report occasions of absenteeism and use of health care services in the past two months. The methods used before and during the trial to encourage correct completion and timely return included: restriction of the diary to one colourful page, piloting among patient and non-patient groups during the development process, provision of a study magnet for attachment to a kitchen appliance, feedback on diary completion during the pre-randomisation run-in, and verbal encouragement during the bimonthly participant retention telephone calls. Acceptability of this novel measurement tool was evaluated by return of a correctly completed Participant Diary within one month of despatch.

Results: At the end of 2008, 317 participants had been randomised for more than one month. Of these, 285 (90%) had returned a correctly completed first Participant Diary (sent at the time of randomisation) within one month. At the end of October 2008, 245 patients had been randomised more than 3 months. Of these, 211 (86%) had returned the second Participant Diary. Similarly, the return rate of the third and fourth Participant Diaries was 156/184 (85%) and 92/112 (82%), respectively. Participants dropping out of the study are included in the denominator of these calculations.

Conclusions: A long development process and regular highlighting/reinforcement of the importance of diary return during routine telephone calls resulted in very high completion and return rates, thereby demonstrating acceptability of this tool.This Participant Diary is able to regularly capture, at low cost, important clinical and health economic outcomes during the course of a long-term clinical trial among people with symptomatic knee OA.

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MAGNETIC RESONANCE IMAGING: AN OPEN-LABEL PILOT STUDY EVALUATING THE DISEASE MODIFYING EFFECT OF CELECOXIB COMPARED TO A MODELIZED HISTORICAL CONTROL COHORT IN KNEE OSTEOARTHRITIS

J.-P. Raynauld[1], J. Martel-Pelletier[1], A. Beaulieu[2], L. Bessette[3], F. Morin[4], D. Choquette[1], B. Haraoui[1], F. Abram[5], **J.-P. Pelletier**[1]
[1]Osteoarthritis Res. Unit, Notre-Dame Hosp.,Univ. of Montreal Hosp. Res. Ctr. (CRCHUM), Montreal, QC, Canada; [2]Faculty of Med., Univ. of Laval, Quebec, QC, Canada; [3]Groupe de recherche en rhumatologie et maladies osseuses, Sainte-Foy, QC, Canada; [4]Ctr. de recherche musculosquelettique, Trois-Rivières, QC, Canada; [5]ArthroVision Inc., Montreal, QC, Canada

Purpose: An open-label 12-month pilot study evaluating the disease modifying effect of continuous treatment with celecoxib 200 mg daily compared to a modelized historical control cohort in the treatment of knee osteoarthritis (OA).

Methods: The primary objective of this study was to evaluate, using magnetic resonance imaging (MRI), cartilage volume changes in the medial compartment of the knee (femoral condyle and tibial plateau) on subjects treated with celecoxib at 200 mg daily (99 patients were recruited; 78 completed the study) for 12 months compared to a modelized historical control cohort (n=89), as expressed by percentage loss from baseline. Secondary outcomes included other cartilage volume assessments including global and lateral compartments as well as knee OA symptoms such as pain, stiffness, and function, as assessed by the WOMAC questionnaire. Safety of the medication was also assessed. The comparison between the two cohorts was evaluated by a multivariate linear regression model.

Results: Cartilage volume loss was not reduced by celecoxib when compared to a modelized historical cohort. Celecoxib provided clinically and statistically significant improvement in symptoms for knee OA patients as shown by the WOMAC scores on pain, stiffness and function. The safety data reported several minor adverse events no different from those typically seen in a one-year clinical trial.

Conclusions: Although celecoxib was demonstrated to be safe and effective for knee OA symptom relief at a daily dose of 200 mg, it did not demonstrate a structural protective effect on knee cartilage. Cohort modelization is an efficient and unbiased way to provide a comparator group for the assessment of novel treatments when classic head-to-head randomized controlled trial is not feasible.

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SHOCKWAVE PROMOTES OSTEOGENESIS OF BONE MARROW STROMAL CELLS IN HIP NECROSIS

C.-J. Wang
Chang Gung Mem. Hosp. at Kaohsiung, Taiwan, Kaohsiung Hsien, Taiwan

Purpose: Bone marrow stromal cells may play an important role in hip necrosis. This in vitro study investigated the osteogenesis effect of extracorporeal shockwave on bone marrow stromal cells in hip necrosis.

Methods: Bone marrow stromal cells were harvested from bone marrow cavity of six patients with hip necrosis. The specimens were divided into four groups including the control, shockwave, shockwave plus L-NAME and shockwave plus NOC18. The control group received no additional treatment. The shockwave group received 500 impulses of shockwave at 14 Kv (equivalent to 0.18 mJ/mm^2). The shockwave plus L-NAME group was pretreated with an inhibitor, L-NAME before shockwave treatment. The shockwave plus NOC18 group consisted of the administration of a promoter, NOC18 and application of shockwave. The evaluation parameters included assessment of cell proliferation (MTT), measurement of alkaline phosphatase level, analysis of VEGF, BMP2, RUNX2 and osteocalcin on real time PCR and von Kossa stain for mineralized nodules.

Results: Significant increases of MTT, alkaline phosphatase, VEGF, BMP2, RUNX2 and osteocalcin and more mature mineralized nodules (Fig. 1) were observed after shockwave treatment as compared to the control. Pre-treatment with L-NAME significantly

The Results of MTT (Cell Proliferation), Alkaline Phosphatase Levels (mMol/ml), VEGF, BMP-2, RUNX-2

	Control	Shockwave	SW+L NAME	NOC18	
MTT (48 hrs)	0.311±0.005	0.352±0.006	0.325±0.006	0.348±0.003	P1: <0.0001 P2: 0.0566 P3: 0.0002 P4: 0.0496
Alkaline Phosphatase Levels (mMol/ml) (72 hrs)	1.537±0.152	2.442±0.156	1.996±0.138	2.438±0.042	P1: 0.001 P2: 0.0867 P3: 0.0065 P4: 0.003
VEGF	1	4.9±0.38	2.26±0.64	4.528±0.12	P1: 0.0154 P2: 0.0945 P3: 0.0252 P4: 0.0006
BMP2	1	1.57±0.18	0.83±0.12	1.46±0.09	P1: 0.0424 P2: 0.1499 P3: 0.0161 P4: 0.0016
RUNX2	1	1.6±0.17	0.93±0.03	1.97±0.19	P1: 0.0371 P2: 0.0918 P3: 0.0283 P4: 0.0065
OCN	1	2.03±0.3	0.93±0.03	2.73±0.29	P1: 0.0366 P2: 0.0918 P3: 0.0319 P4: 0.0134